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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/29/04 has been entered.

2. The amendment has been entered. Claims 1-5 have been amended. Claims 10-16 have been added. Claims 1-16 are presently and are addressed herein.

3. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is drawn to the method of any of claims 1-4 wherein the HSV genome comprises an insertion of an expressible non-natural protein coding sequence... It is noted that the specification does not define the metes and bounds of the term "non-natural protein". As such it is unclear what exactly is a non-natural protein. For instance, it is unclear if a non-natural protein is one that is not found in the wild-type HSV genome, or if it encompasses encoding a protein made of "non-natural" amino acids, or if it means something completely different than these two possibilities. It is noted that claims 1-4 are independent claims from which claim 15 depends. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing "non-natural protein".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

8. Claim 5 is drawn to the method of claim 1, 2, 3, or 4 wherein the modified HSV genome further comprises deletion of a gene selected from a large group (see claim 5).

However, looking to the specification, it is clear that claim 5 encompasses genes that were not disclosed in the specification. Specifically, the Examiner can only find support for the following genes: UL16, UL24, UL40, UL41, UL55, UL56, alpha22, US4, US8 and US11. Support cannot be found for the other genes. The Applicants are asked to specifically identify where, by page and line number, support for the other genes can be found.

9. Claim 15 is drawn to the method of any of claims 1-4 wherein the HSV genome comprises an insertion of an expressible non-natural protein coding sequence... Looking to the specification, support for an HSV vector comprising an insertion of an expressible non-natural protein cannot be found. The Applicants are asked to specifically identify where, by page and line number, support for the vector comprising a sequence encoding a non-natural protein can be found.

10. It is noted that claims 1-4 are independent claims from which claims 5 and 15 depend. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing the limitations for which there is no support found in the specification.

11. Claims 1-4 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection**.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

The instant claims are drawn to a method of treatment (claims 1-4) wherein an HSV vector comprising an insertion of an expressible non-natural protein coding sequence (claim 15) is administered to a subject having cancer. It is noted that the claims encompass encoding any protein that could be considered "non-natural". However, as indicated above, the term "non-natural protein" has not be defined in the specification. Therefore the claims encompass a myriad of proteins however the specification has not disclosed a single species of this large genus of proteins. There is no indication of the any "non-natural protein" by name or by sequence. Furthermore, applicants have not identified any structural characteristics common to all species of the genus. As such the specification has not adequately described a representative number of non-natural proteins encompassed by the claims.

It is noted that claims 1-4 are independent claims from which claim 15 depends. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing "non-natural protein".

12. Additionally, claims 1-4 and 15 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement—in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As indicated above, the claims encompass a genus of molecules (specifically "non-natural proteins") which re not adequately described in the specification. Since the specification has not adequately describe the "non-natural proteins" encompassed by the claims, one of skill in the art would not know how to make/use the invention without performing an undue amount of additional experimentation.

13. Claims 1-9 remain rejected and new claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for reducing tumor mass by directly injecting an HSV that expresses only one gamma(1)34.5 gene product into a tumor in an amount effective to reduce the mass of said tumor;

14. does not reasonably provide enablement for treatment in an individual via any route of administration other than direct injection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims, for the reasons of record, which are reiterated below for convenience.

The following factors have been determined by the courts to be critical in determining whether a claimed invention is enabled (See In re Wands 8 USPQ 2d 1400, Fed. Cir. 1988).

The nature of the invention: The instant claims are drawn to a method for reducing tumor mass in an "individual" comprising administering an amount of recombinant Herpes simplex virus (HSV) wherein said HSV genome comprises a modification of an inverted repeat region such that one $\gamma_1$34.5 gene remains intact and where in said amount of HSV is being effective to reduce tumor mass. Thus, the nature of the invention is a therapeutic use of attenuated HSV virus for treating tumors and generally falls in the realm of gene therapy, and specifically encompasses oncolytic virotherapy.

The state of the prior art and the predictability or unpredictability of the art: At the time of filing, the relevant art considered gene therapy as a whole to be extremely unpredictable. Efficacious, predictable modes of delivery that would provide efficient delivery and expression of genes encoding the protein in the target cells had not been developed. Regarding the specific delivery of therapeutic viruses to targeted cells, **Verma et al.,** (1997) states that delivery is the "Achilles heel", and indicates, "[t]he use of viruses is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses" (pg. 293, col. 3, parag. 1). **Chamber** et al., (1995) previously attributed the greater survival benefit for glioma-bearing mice treated with a $\gamma_1$34.5 mutant in which the 34.5 gene is interrupted by a stop codon (R4009) rather than

by deletion (R3616) due to the low level of stop codon suppression in R4009 allowing for enough viral replication so as to effectively destroy tumor cells, yet not multiply to a level where it can cause encephalitis and taught that the "key to the development of effective oncolytic viruses may well depend on precise control of the expression of the $\gamma_1$34.5 gene" and that "this observation may be exploited to construct still more effective viruses" (page 1415, left column). **Advani** (1998) teaches that "While attenuated herpes viruses alone have not been tested in humans, the available data in experimental animals do not predict a high cure rate (page 162, left column) and that "infection alone produced few cures and the majority of infected tumors either grew more slowly or outpaced cell destruction" (page 162, top right column). **Crystal** (1995) has previously recited that "human are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (page 409, bottom, left column). Without an art recognized nexus between the results obtained in animal models and the results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

Specifically regarding the use of nude mice as human cancer models, Trisha **Gura** teaches in her article titled "Systems for identifying new drugs are often faulty" (Science, 1997; 278:1041-1042),

> "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does." (See p. 1041, first column)

Gura also teaches, "xenografts tumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues for example. Thus, drugs tested in the xenografts appeared effective, but worked poorly in humans." (See p. 1041, column 2).

Furthermore, **Kerbel** teaches (see "What is the optimal rodent model for anti-tumor drug therapy?" Cancer and Metastasis Reviews Vol. 17:301-304; 1999), "A recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans." (See p. 301, first column). Kerbel indicates a number of specific problems with the mouse model, including (i) concentrations of drugs are used at the maximum tolerated doses for mice, not humans—it turns out that the maximum tolerated dose for mice is often significantly greater than it is for man (see p.301, first column); (ii) most transplanted tumors are very fast growing—drugs are often designed to target rapidly dividing cells; however, natural human tumors often grow much slower. Therefore, the transplanted tumors can show an "exaggerated" response to a drug (see p. 301, second column); and (iii) the response to therapy of a single 'primary' growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases. Regarding (iii), Kerbel teaches, "Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery." (See p. 302, column 1).

Additionally, the claims encompass treating any type of tumor by any route of administration. Therefore, the claims encompass treating CNS tumors, such as

glioblastomas, by administering the HSV intravenously, subcutaneously, etc. Clearly systemic administration of the HSV (such as by intramuscular, intravenous, or subtaneous administration) would have no efficacy against glioblastoma, wherein the blood-brain barrier restricts entry of 120nm HSV particles into the brain (**Muldoon** et al. Am. Journ. Pathol. 147(6):1840-1851, 1995).

The above references acknowledge the usefulness of gene therapy for the treatment of cancer and other diseases in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome.

The breadth of the claims and the amount of direction or guidance presented in the specification and the presence or absence of working examples:

As such, the disclosed claims are very broad and read on killing any type of tumor by delivering the attenuated HSV by any route to an individual. Clearly, systemic administration of an attenuated oncolytic herpesvirus by intramuscular injection will have little or no efficacy against a glioblastoma, wherein the blood brain barrier restricts entry into the brain of 120 nm HSV particles (**Muldoon** et al., 1995). Furthermore, there is a lack of reference between the in vivo nude mouse model data presented by applicants and results which skilled artisan would expect in humans. That is, there is no example or guidance in the specification that would indicate or guide the skilled practitioner on modifying the treatment of the nude mouse to a human that has a functional immune system. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat glioblastoma, prostate adenocarcinoma and hepatoma in the individual.

The quantity of experimentation: To attempt to practice the claimed invention in humans, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art (as indicated above), also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one of skilled in the art would resort to trial and error experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the full scope of the claims is very high and is in fact undue.

Response to Arguments

15. Applicant's arguments filed 3/29/04 have been fully considered but they are not persuasive. Applicants argue that the Examiner has misperceived the significance of the Koobey and Walker references that were cited by the Applicants in response to the

enablement rejection. The applicants assert that the Kooby and Walker references confirm the assertion that HSV, including modified HSV, may be effectively administered by any number of routes. Thus, Applicants contend, one of skill in the art would reasonably expect the modified HSV recited in the pending claims to be deliverable by any known route, and the Examiner has not provided evidence inconsistent with that position. Rather, applicants assert, the Examiner has focused on the potential effects of such modified HSVS on non-cancerous cells and asserted that such effects would not be shared by the modified HSVS of Kooby or Walker. That assertion is not relevant to the question of enablement, however. The applicants also argue the rejection as it based on the insufficient written description of gene alterations that would result in an HSV that only expresses a single gamma(1)34.5 gene.

In response, it is first noted that the rejection of claims based on an the insufficient written description of gene alterations that would result in an HSV that only expresses a single gamma(1)34.5 gene are moot, as the written description rejection has been withdrawn. Applicants' arguments with respect to one of skill having the knowledge to make modifications to the HSV genome such that it resulted in an HSV that only expresses a single gamma(1)34.5 gene are persuasive.

However, regarding the arguments with respect to the rest of the enablement rejection, Applicants arguments are not persuasive. It is acknowledged that Kooby and Walker are different from the instantly claimed HSV. It is also accepted that although the instantly claimed HSV may cause deleterious effects on normal cells, this does not indicate that the method would not also result in a reduction of tumor mass, as claimed. However, there are a number of significant differences between the examples of Kooby

and Walker and the instant invention. For example, Kooby (as previously indicated by Applicants) does teach inhibiting the growth of tumor metastasis in the liver of a rat by administering an HSV via portal vein injection. However, it is respectively pointed out that tumor metastases in the liver would mean that the tumors are spread throughout the liver, and not necessarily in a confined area of the liver. Furthermore, administration to the liver via portal vein injection, is not representative of systemic administration, as are the instant claims. The portal vein leads directly into the liver. Therefore, it would be expected that administering an HSV via portal injection would result in the HSV infecting the liver cells, including the liver metastases. This is different from systemic administration (encompassed by the claims) wherein the HSV is administered intramuscularly, subcutaneously, etc (such as at a distal site) and resulting in infection of the appropriate target tissue. It is noted that portal vein delivery to tumors in the liver is considered a "local" administration rather than systemic administration. However, the specification does not appear to have support for "local administration" as it pertains to portal vein delivery to the liver (or delivery to a specific target by administering the HSV to the local blood vessels). The only support found in the specification for "local delivery" is by direct injection of the HSV into the target tumor. As such the claims are enabled for direct delivery (such as direct injection) of the HSV into the target tumor. With respect to the reference that teaches treating a subcutaneous tumor in a nude mouse by tail vein injection of the HSV composition, it is respectfully pointed out that the animal is a nude mouse that has a compromised immune system. As such, the nude mouse is not an appropriate model for systemic delivery of an HSV to a distal tumor in animals that have a functional immune response, such as larger animals and humans. As

previously indicated, Verma teaches that "humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses" (pg. 293, col. 3, parag. 1). Therefore, it is unpredictable that the HSV could be administered systemically to an animal/human with a functional immune system and expect the administration to inhibit tumor growth of a distal tumor. It is noted that the nude mouse having a xenograft tumor is an appropriate animal model for direct delivery of an HSV to a tumor, as the immune response in a in an animal with a functional immune system would be directed against the infected tumor cells. Furthermore, applicants are respectfully reminded that the claims are very broad and encompass administering a HSV to an individual by general administration and inhibiting the growth of CNS tumor, such as a glioblastoma. As previously indicated, systemic administration of the HSV (such as by intramuscular, intravenous, or subtaneous administration) would have no efficacy against glioblastoma, wherein the blood-brain barrier restricts entry of 120nm HSV particles into the brain (**Muldoon** et al. Am. Journ. Pathol. 147(6):1840-1851, 1995). It appears that the applicants' only rebuttal to this is that "the statute does not require 'a specific example of everything within the scope of a broad claim.' In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973)." It is acknowledged that not every single scope of a broad claim must be proven enabled. However, when there is teaching in the art indicating that there problems with respect to the predictability of a particular aspect of the claimed invention, applicants need to rebut the teachings of the art. Here, the art indicates that it would be unpredictable to systemically administer an HSV to a immune-competent animal and expect to inhibit the growth of a brain tumor, such as glioblastoma. Applicants have overcome this teaching.

Furthermore, it is respectfully pointed out that both of the references (Kooby and Walker) Applicants cited to overcome the enablement rejection as it applies to systemic delivery of the HSV, were published after the effective filing date of the instant application. Applicants are respectfully reminded that the application must be enabling at the time filing, either through the disclosure in the specification, or through the specification in view of the prior art. Since Kooby and Walker are not prior art, they are not appropriate references because they do not indicate that the invention was enabled at the time of filing.

Therefore, the enablement rejection is not withdrawn. It is noted, however, that the claims are enabled for direct delivery as indicated above. Limiting all claims to direct delivery of the HSV to the tumor would obviate this rejection.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-5, 7, 9-12 an 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys) or alternatively Advani (Feb. 1998; Gene Therapy) (both previously cited).

It is noted that this rejection was previously pending and withdrawn; however, upon further consideration, the rejection is deemed to be appropriate and the rejection is herein set forth again.

The instant claims are drawn to a method for reducing tumor mass by administering an attenuated HSV to a subject having cancer wherein the HSV genome has been modified in an inverted repeat region such that the HSV has only one active gamma(1)34.5 gene, wherein the HSV is administered in an amount effective to reduce tumor mass. It is noted that the claims explicitly encompass administering HSV R7020, and the claims explicitly encompass administering the HSV to CNS tumors.

Advani (1997) is an abstract that clearly teaches "Human U-87MG glioma cells were grown in the hind limb of athymic mice... and infected with... [HSV] R7020... the tumors were harvested... 14 days after viral injection." Furthermore, Advani teaches, "Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." (emphasis added). Therefore, Advani (1997) clearly anticipates the instant claims as they encompass a method for reducing tumor mass comprising direct delivery of the attenuated HSV to the tumor.

Similarly, Advani (1998) also teaches the same data with more detail, as it is a complete journal article rather than an abstract. Advani (1998) teaches a number of different experiments wherein HSV R3616 is directly administered to human glioma xenografts in nude mice by itself, and in combination with other agents (e.g., see Fig.1, Fig. 2). The injected tumors were allowed to grow and then there volume was measured at different time points (Figs 1 and 2). Avani specifically teaches, "the experiment was

repeated with R7020, another genetically engineered attenuated virus" (see p. 161, bottom of second column), indicating that the R7020 was also injected into glioma xenografts in a nude mouse model and tumor volume was measured at certain time points.

Applicants have previously argued that the references do not teach that method results in a reduction of tumor mass, as required by the claims. Specifically, Applicants argued,

> "Advani 1997 and 1998 disclose the same data as found in Figure 3 of Advani 1998, but neither reference discloses that the R7020 virus is able to kill tumor cells at a rate that is greater than the tumor is able to grow which is necessary to result in reduced tumor mass. Because anticipation requires that every limitation of the claims be found in the cited art, neither... the Advani references can anticipate the claimed invention and the rejections must be withdrawn." (See response filed 7/19/02).

However, it appears that both Advani references teach a method wherein HSV R7020 is administered to an animal having a CNS tumor by directly injecting the HSV into the tumor. It also appears that the injected tumors were analyzed (i.e. volume was measured) up to (at least) 14 days after injection of the HSV. It is acknowledged that the references do not explicitly teach that the administration of HSV R7020 resulted in a reduction of tumor mass. However, the references do teach all of the steps using all of the claimed materials. As such, the method taught by Advani (1997) and Advani (1998) would inherently result in the reduction of tumor mass.

It is noted that MPEP 2112 states,

> "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. 'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.' In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782,

> 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983)... The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)... 'In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)"

Additionally, MPEP 2112.02 states,

> "Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986)"

In the instant case, the prior art "device" is the HSV R7020 and in its normal and usual operation would necessarily perform the method claimed. Therefore, the instant claims are clearly anticipated by Advani (1997) and separately by Advani (1998).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys) in view of Carroll et al. (Ann. Surg. 1996); or alternatively Advani (Feb. 1998; Gene Therapy) in view of Carroll et al. (Ann. Surg. 1996).

Advani (1997) and Advani (1998) both, separately teach a method for reducing tumor mass as previously indicated (see above rejection).

Neither Advani (1997 or 1998) teach that the attenuated HSV virus could be used to treat a non-CNS tumor.

Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for treating colon carcinoma liver metastasis by administering an attenuated HSV directly to the tumor (e.g., see abstract).

Therefore, it would he been prima facie obvious at the time of invention that the method taught by Advani (1997) or Advani (1998) would have also been able to treat a non-CNS tumor such as a colon carcinoma liver metastasis in an animal or human, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the method Advani (either 1997 or 1998) to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE T. NGUYEN
PRIMARY EXAMINER

Jon Eric Angell, Ph.D.
Art Unit 1635